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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/921,819	08/03/2001	Roland Buelow	39691-0005A	8351

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EXAMINER	
WEHBE, ANNE MARIE SABRINA	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 03/25/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/921,819	BUELOW ET AL.	
	Examiner	Art Unit	
	Anne Marie S. Wehbe	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 December 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *13-30,67-72 and 76* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13-30,67-72 and 76* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response to the notice of non-responsive amendment received on 12/16/04 has been entered. Applicant's election without traverse of SEQ ID NO: 10 is acknowledged. As noted in the notice of non-responsive amendment, applicant's previous amendment filed on 9/3/04 added new claims 67-76. In the present amendment filed on 12/16/04, claims 1-12, 31-66, and 73-75 are canceled. Claims 13-30, 67-72, and 76 are currently pending and under examination in the instant application. An action on the merits follow.

Those sections of Title 35, US code, not included in this action can be found in the previous office action.

Information Disclosure Statement

The information disclosure statements filed on 7/15/04 and 10/25/04 have been considered. However, in regards to the WO 97/18,703 and H6-16698 documents listed on the 1449 submitted on 7/15/04, please note that these references have only been considered based on the English language abstract or translation provided with these documents. Copies of the signed and dated 1449s are attached to this action.

Claim Rejections - 35 USC § 102

The rejection of claims 13-30 are rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent Application Publication 2002/0028488 (3/7/02), hereafter referred to as Singh et al. , is withdrawn in view of applicant's amendments to the claims to recite that the non-human animal is "other than a bird".

The following rejections have been necessitated by applicant's amendments to the claims.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 13-26 and 67-71 are rejected under 35 U.S.C. 102(b) as being anticipated by U.S. Patent No. 5,569,825 (1996), hereafter referred to as Lonberg et al. The applicant claims transgenic vectors comprising a humanized Ig locus which comprises a portion of an Ig locus of a non-human mammal and at least one human Ig gene segment in unrearranged, partially rearranged or fully rearranged configuration, wherein the humanized locus is capable of undergoing gene conversion in a non-human animal. The claims further recite wherein the non-human animal is a chicken, wherein the humanized locus is a heavy chain locus which comprises at least one V gene segment, one D gene segment, one J gene segment, and a human heavy chain

constant region gene segment, preferably the human Cγ gene segment. Other claims recite wherein the humanized locus is a light chain locus which comprises at least one V gene segment, one D gene segment, and a human light chain constant region gene segment, preferably the human kappa or lambda constant gene segments. The applicant also claims wherein the vector comprises about 10-100 V gene segments, where the segments are selected from V gene segments at the 3' V-region of the non-human animal and human V gene segments. In addition, the applicant claims a transgenic vector comprising a humanized Ig locus, wherein regulatory sequences of the locus are from the non-human animal, wherein the locus comprises two or more Ig gene segments encoding human Ig polypeptide sequences flanked and separated by non-coding sequences from the non-human animal, and wherein the Ig segments are in unrearranged, or rearranged configuration.

Lonberg et al. teaches plasmid vectors encoding transgenes comprising a humanized heavy chain immunoglobulin locus in rearranged or unrearranged configuration comprising between 1-100 human heavy chain variable region gene segments, between 1-50 human heavy chain D region gene segments, between 1-50 human heavy chain J region gene segments, and between 1-10 human heavy chain C region gene segments (Lonberg et al., column 3, and columns 18-19). Lonberg et al. further teaches similar transgenes comprising human kappa light chain V, D, and C gene segments (Lonberg et al., column 15). Lonberg et al. teaches that these transgenes are useful for generating transgenic non-human animals capable of producing human antibodies, specifically transgenic bovines, ovines, and rabbits, rabbits being a particularly preferred animal (Lonberg et al., column 10, lines 46-60). In addition, Lonberg et al. teaches that the non-coding switch regions flanking the constant region gene or genes are derived from those

that occur naturally in the germline of the species that is to receive the transgene construct, i.e. a rabbit, and further that additional regulatory sequences in the transgene are also derived from the non-human animal (Lonberg et al., column 8, lines 19-21, and column 9, lines 3-6). In addition, Lonberg et al. teaches that a preferred human constant region to include in the transgene is the human Cγ1 gene segment (Lonberg et al., column 19, lines 15-17). Thus, by teachings transgene vectors comprising all the limitations of the claims as written, Lonberg et al. anticipates the instant claims.

Claim 76 is rejected under 35 U.S.C. 102(a) as being anticipated by Rader et al. (May, 2000) J. Biol. Chem., Vol. 275, No. 18, 13668-13676. The applicant claims a transgenic vector comprising a humanized Ig locus wherein at least 90% of the locus is identical to the sequence of the Ig locus of a non-human animal, wherein said humanized Ig locus comprises a least one Ig gene segment encoding human immunoglobulin polypeptide sequences flanked and separated by non-coding sequences of the non-human animal, and wherein the gene segments are rearranged, partially rearranged, or unrearranged.

Rader et al. teaches a plasmid comprising a transgene encoding the rabbit rearranged V_L or V_H region which comprises a V gene segment and a J gene segment for the light chain and a V gene segment, a D gene segment, and a J gene segment for the heavy chain, wherein the V region has been humanized to contain human polypeptide sequences (Rader et al., page 1366, column 2, paragraph 2, and Figure 2). From figure 2 it is apparent that more than 90% of the resulting transgene is derived from the rabbit (Rader et al., page 1367). Further, since only the

coding sequences were humanized, the remaining sequences are derived from the rabbit. Thus, by teaching all the limitations of the claims as written, Rader et al., anticipates the instant claim.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 27-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,202,238 (1993), hereafter referred to as Fell et al., in view of Rader et al. (May, 2000) J. Biol. Chem., Vol. 275, No. 18, 13668-13676. The applicant claims methods of making a transgenic vector comprising (i) obtaining a DNA fragment comprising an Ig locus from a non-human animal other than a bird which comprises at least one V gene segment, one J gene

segment, and one constant region gene segment and (ii) integrating at least one human Ig gene segment into the said DNA fragment. The applicant further claims said method wherein the integration is by homologous recombination in a non-human animal cell, yeast, or bacteria.

Fell et al. teaches making a transgenic vector by providing a phage containing the entire mature gene encoding a murine heavy chain and co-transfecting murine cells with this vector and a second targeting vector which comprises of regions of homology to the fourth joining region and enhancer of the mouse heavy chain gene flanking the human gamma 1 constant region gene such that the constant region of the mouse heavy chain is replaced by the human constant region by homologous recombination (Fell et al., column 14, example 6, and Figure 1). Fell et al. teaches that most monoclonal antibodies are made in mice and therefore have limited use in humans because they are recognized as "foreign". Fell et al. teaches that the purpose of including human gene segments in the murine antibodies is to reduce immune responses against these antibodies in humans (Fell et al., column 2).

While Fell discloses a generic method for making chimeric antibodies, the specific examples are to murine antibodies. However, Rader et al. supplements Fell et al. by providing motivation for making chimeric rabbit antibodies over murine antibodies. Rader et al. teaches that,

> "compared with the other existing sources of human or humanized antibodies, immune rabbits are an attractive alternative for several reasons...epitopes that are not immunogenic in mice, a species from which the vast majority of monoclonal antibodies to human antigens has been generated, might be immunogenic in rabbits. This is of particular interest for the development of therapeutic human antibodies that are evaluated in mouse models and are required to recognize both the human antigen and its mouse homologue" (Rader et al., page 13674, column 2).

Rader et al. also teaches that the rabbit Ig gene repertoire is well characterized (Rader et al., page 13674, column 2). Therefore, in view of the specific advantages of producing humanized antibodies in rabbits over mice as taught by Rader et al., it would have been *prima facie* obvious to the skilled artisan at the time of filing to follow the methods of Fell et al. using rabbit immunoglobulin loci instead of mouse immunoglobulin loci. Further, in view of the fact that the rabbit Ig gene repertoire is well characterized, and the high level of skill in the art of molecular biology at the time of filing, the skilled artisan would have had a reasonable expectation of success in replacing a rabbit constant gene segment with a human gene segment according to the methodology taught by Fell et al.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 67-72 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 67 recites on line 4, "human immunoglobulin polypeptide sequences franked and separated". The word "franked" is confusing and appears to be a typographical error. Appropriate correction is required. Claims 68-72 depend on claim 67 and thus are included in this rejection.

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (571) 272-0737. The examiner can be reached Monday- Friday from 9:30-6:00 EST. If the examiner is not available, the examiner's supervisor, Ram Shukla, can be reached at (571) 272-0735. For all official communications, **the new technology center fax number is (571) 273-8300**. For informal, non-official communications only, the examiner's direct fax number is (571) 273-0737.

Dr. A.M.S. Wehbé

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER